Applicants note the objections to the drawings, including those raised in the attachment to Paper # 5, but prefer to delay the filing of corrected formal drawings until after allowable subject matter is indicated.

Specification

Applicants were requested to amend the specification by indicating whether the instant application is "a CIP, DIV, or CON" of applications 08/804,444 and 09/012,116. Applicants were further invited to correct the address of ATCC at page 131, line 5. The foregoing amendments of the specification serve the make these corrections.

Claim Rejections - 35 U.S.C. § 112

(1) Claims 1-17 and 32-33 were rejected under 35 U.S.C. §112, second paragraph, as "being indefinite" in their recitation of the term "nonproteinaceous polymer." According to the rejection, a "nonproteinaceous polymer can be anything, an organic molecule, an inorganic molecule, a DNA fragment, a plastic, a carbohydrate, etc." The Examiner cited *Ex parte* Tanksley (26 USPQ2d 1384) (Bd. Pat. Appl. & Int., 1992) for the notion that "the claims must be so definite as to allow the comparison with the available art and must also make it possible for the public to determine from the claims what they encompass."

Applicants submit that the rejected claims meet the statutory standard set forth in 35 U.S.C. § 112, second paragraph, by particularly pointing out and distinctly claiming the subject matter which they consider as their invention. A definition of the term "nonproteinaceous polymer" is provided at page 12, lines 32-37 of the specification.

According to this definition:

> "Unless specifically indicated to the contrary, the terms "polymer", "polymer molecule", nonproteinaceous polymer", and "nonproteinaceous polymer molecule" are used interchangeably and are defined as a molecule formed by covalent linkage of two or more monomers, wherein none of the monomers is contained in the group consisting of alanine (Ala), cysteine (Cys), aspartic acid (Asp), glutamic acid (Glu), phenylalanine (Phe), glycine (Gly), histidine (His), isoleucine (Ile), lysine (Lys), leucine (Leu), methionine (Met), asparagine (Asp), praline (Pro), glutamine (Glu), arginine (Arg), serine (Ser), threonine (Thr), valine (Val), tryptophan (Trp), and tyrosine (Tyr) residues."

In the rejected claims, the nonproteinaceous polymer is described as part of a heterogeneous molecule (conjugate), in which it is covalently attached to one or more antibody fragment, where the resultant conjugate is water soluble, i.e. is soluble in physiological fluids such as blood, and wherein the heterogeneous molecule is free of any structured aggregate (page 12, lines 20-24). The phrase "structured aggregate" is in turn defined as:

> "(1) any aggregate if molecules in aqueous solution having a spheroid or spheroid shall structure, such that the heterogeneous molecule is not in a micelle or other emulsion structure, and is not anchored to a lipid bilayer, vesicle or liposome; and (2) any aggregate of molecules in solid or insolubilized form, such as a chromatography bead matrix, that does not release the heterogeneous molecule into solution upon contact with an aqueous phase."

Accordingly, by the definitions provided in the specification, the nonproteinaceous polymer cannot be "anything," rather is a polymer in which the monomeric subunits are not selected from the listed amino acid residues (i.e. it is not a protein), and which, when covalently linked to one or more antibody fragments, results in a product (conjugate) that is soluble in water and in physiological fluids.

The disclosure at pages 39-42 provides further guidance for identifying the nonproteinaceous polymers that fall within the scope of the present invention. This disclosure further elaborates on the definition, and specifically lists a large number of nonproteinaceous polymers the use of which is contemplated.

Furthermore, according to well established rules of claim construction, "[a] technical term . . . is interpreted as having the meaning that it would be given by persons experienced in the field of the invention." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (quoting *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996)); *see also* Manual of Patent Examining Procedure (M.P.E.P.) § 2111.01 ("[T]he words of a claim . . . must be read as they would be interpreted by those of ordinary skill in the art."). Accordingly, unless otherwise specified, a claim term should be given a meaning that is consistent with the meaning given that term in other contemporary patents from the related art. *See In re Cortright*, 165 F.3d 1353, 1358 (Fed. Cir. 1999) ("[I]nterpretation of claim terms should not be so broad that it conflicts with the meaning given to identical terms in other patents from analogous art.").

By searching the patent database of the United States Patent and Trademark Office, applicants found 62 issued United States patent disclosing and definition the term "nonproteinaceous polymer." According to a definition common to most of these patents, including U. S. Patent No. 6,270,987 (earliest priority claimed: January 31, 1997):

> "The nonproteinaceous polymer ordinarily is a hydrophilic synthetic polymer, i.e., a polymer not otherwise found in nature. However, polymers which exist in nature and are produced by recombinant or in vitro methods are useful, as are polymers which are isolated from nature. Hydrophilic polyvinyl polymers fall within the scope of this invention, e.g., polyvinylalcohol and polyvinylpyrrolidone. Particularly useful are polyvinylalkylene ethers such as a polyethylene glycol, polypropylene glycol."

Similarly, according to U. S. Patent No. 6,252,051 (earliest priority claimed: July 9, 1997):

> The ***nonproteinaceous polymer*** ordinarily is a hydrophilic synthetic polymer, i.e., a polymer not otherwise found in nature. However, polymers which exist in nature and are produced by recombinant or in vitro methods are useful, as are polymers which are isolated from native sources. Hydrophilic polyvinyl polymers fall within the scope of this invention, e.g. polyvinylalcohol and polyvinylpyrrolidone. Particularly useful are polyalkylene ethers such as polyethylene glycol (PEG); polyelkylenes such as polyoxyethylene, polyoxypropylene, and block copolymers of polyoxyethylene and polyoxypropylene (Pluronics); polymethacrylates; carbomers; branched or unbranched polysaccharides which comprise the saccharide monomers D-mannose, D- and L-galactose, fucose, fructose, D-xylose, L-arabinose, D-glucuronic acid, sialic acid, D-galacturonic acid, D-mannuronic acid (e.g. polymannuronic acid, or alginic acid), D-glucosamine, D-galactosamine, D-glucose and neuramninic acid including homopolysaccharides and heteropolysaccharides such as lactose, amylopectin, starch, hydroxyethyl starch, amylose, dextrane sulfate, dextran, dextins, glycogen, or the polysaccharide subunit of acid mucopolysaccharides, e.g. hyaluronic acid; polymers of sugar alcohols such as polysorbitol and polymannitol; heparin or heparon. The polymer prior to cross-linking need not be, but preferably is, water soluble, but the final conjugate must be water soluble. In addition, the polymer should not be highly immunogenic in the conjugate form, nor should it possess viscosity that is incompatible with intravenous infusion or injection if it is intended to be administered by such routes.
>
> Preferably the polymer contains only a single group which is

> reactive. This helps to avoid cross-linking of protein molecules. However, it is within the scope herein to optimize reaction conditions to reduce cross-linking, or to purify the reaction products through gel filtration or chromatographic sieves to recover substantially homogenous derivatives.
>
> The molecular weight of the polymer may desirably range from about 100 to 500,000, and preferably is from about 1,000 to 20,000. The molecular weight chosen will depend upon the nature of the polymer and the degree of substitution. In general, the greater the hydrophilicity of the polymer and the greater the degree of substitution, the lower the molecular weight that can be employed. Optimal molecular weights will be determined by routine experimentation.

These definitions are fully consistent with the definition and other related disclosure provided in the specification, and represent an art recognized definition at and around the effective filing date of the present application. Accordingly, a person skilled in the art would clearly understand the metes and bounds of invention claimed, based on general knowledge in the art at the time of making the present invention, and also in view of the definition provided in the specification, which is fully consistent with the art known and accepted meaning of the term.

This is a very different situation from the issues considered by the Board of Patent Appeals and Interferences in *Ex parte Tanksley*. There, the claims at issue were directed to a series of cDNA clones isolated from a large quantity of random clones produced from mRNA and genomic RNAs, which were referred to merely by an alphanumeric designation. The specification did not set forth the relative positions of the chromosome map of the various clones in the collection, and did not include the sequences of the clones. Under these extreme circumstances, the Board found that the claims did not describe the invention in terms which would have enabled its comparison with the prior art, and did not enable a potential infringer to determine whether infringement in fact occurred without undue burden. This is very different from the present situation where the definitions provided in the specification, and general knowledge in the pertinent art, clearly enable the public to establish the boundaries of the protection sought without undue burden.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claim 14 was rejected for reciting "derived from a parental antibody" for, in the Examiner's view, the term "derived" does not have a universally accepted meaning in the art, nor is it adequately defined in the specification. Without acquiescence in the rejection, claim 14 has been amended to eliminate this term, which obviates the present rejection.

(3) Claim 14 was rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement as to how to make and/or use the invention. According to the rejection, while the "specification teaches a general method for covalent attachment of a nonproteinaceous polymer to a cysteine residue," it "does not enable the production of functional antigen binding fragment as broadly claimed. " The Examiner notes that especially amino acids with bulky side chains might not be tolerated and result in proper folding and packing of the heavy and light chains in the absence of the disulfide bond in the antibody. Furthermore, the Examiner finds that "the specification fails to teach an example where the disulfide bond linking the cysteine residues in the light or heavy chain is substituted for an amino acid and the cysteine is covalently coupled to a nonproteinaceous polymer that results in a functional antibody." Finally, the Examiner refers to Figure 1 of Winter (EP 0239400) as allegedly illustrating that "it is not clear which disulfide bond connecting the heavy and light chains can be used as claimed and obtain a functional antibody." The Examiner concludes that "undue experimentation would be required to make and use the instantly claimed antibody fragments."

Applicants respectfully disagree.

The rejection is based on the assumption that the conjugates of the present invention must retain the proper three-dimensional structure of a non-derivatized parent antibody to be useful. This is not the case. As noted at page 44, lines 1-6, the increased half-life of the conjugates of the invention can also be applied advantageously for allergen tolerization. Even if one assumes that any conformational perturbation originating from the amino acid substitution recited in claim 14 disrupts a conformational epitope, such conformational change will not alter linear epitopes. Such linear epitopes would still be useful in allergen tolerization. In fact, even immunization with a conformationally perturbed species would provide valuable information to a researcher interested in identifying those portions of an antibody fragment that do not contribute to conformational epitopes that are recognized as foreign antigens in a particular animal model. Such information would be useful in the development of a "deantigenized" antibody fragment in a particular animal model.

Furthermore, the teaching of the specification should be read against general knowledge in the art. A specification need not disclose what is well known in the art. See, *e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986).

The court in *In re Wands* stated: "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." . *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988), (quoting *In re* Jackson, 217 U.S.P.Q. 804, 807 (BNA)). The question whether the practice of an invention would require undue experimentation is evaluated by analyzing the *In re Wands* factors, referred to but not analyzed in the rejection. These factors include the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art.

The state of the art

The state of the art of amino acids, including their structure, size, configuration, is extensive. It is well known which amino acids have bulky side chains, and which amino acids can usually be substituted for each other without significant adverse consequences (e.g. conservative amino acid substitutions.

The level of ordinary skill

It is well established that the level of ordinary skill in the art of biotechnology is extremely high, and is represented by the knowledge of a Ph.D. scientist, who is also knowledgeable in the subdiscipline of the invention and skilled in that subdiscipline's routine techniques. See *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372-74 (Fed. Cir. 1999).

The level of predictability in the art

Although the level of unpredictability in the art of biotechnology is generally high, this is not necessarily true for the effect on amino acid substitutions on the conformation of proteins, e.g. antibody fragments. The reason for this is the extensive knowledge about both amino acids and amino acid substitutions and about antibody art.

Accordingly, a person skilled in the art would well know which amino acid substitutions to avoid if the functionality of the antibody fragments within the conjugates of the present invention were to be preserved. As the Examiner has correctly noted "[o]ne skilled in the art would conclude that not every amino acid, especially those that have bulky side chains, would be

tolerated and result in proper folding and lacking of the heavy and light chains in the absence of the disulfide bond in the antibody." Based on this conclusion, one skilled in the art would not make these substitutions when trying to make fully functional antibodies. On the other hand, the same skilled person would be open to such substitutions in instances when potential conformational perturbances are acceptable.

In view of the foregoing arguments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Priority

Applicants note that the priority of the filing date of U.S. application Serial No. 09/012,116 (January 22, 1998) has been accorded to claims 1-34 pending in this application.

Double Patenting

Claims 1-34 of the present application were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-37 of copending Application Serial No. 09/489,394. Claims 1, 10-12, and 14 were further provisionally rejected under the same judicially created doctrine over claims 1, 5, 6, 7, 19, 26-27 of copending Application Serial No. 09/234,182.

Applicants believe that upon entry of the present Amendment and consideration of the arguments presented, these will be the only rejections remaining in the present application. Accordingly, the Examiner is requested to withdraw both provisional obviousness-type double patenting rejections in the present case, allow the present application, and repeat the double patenting rejections, if appropriate, in parallel applications 09/489,394 and 09/234,182, respectively.

Claims Rejections - 35 U.S.C. § 102

(1) Claims 1-7 were rejected under 35 U.S.C. § 102(b) as "being anticipated by Wilcheck et al. (Methods in Enzymology 104 pages 3-8, 10-11, 17-18, 1984)." Wilcheck was cited for its disclosure of immunoaffinity chromatography and methods of covalent attachment of antibodies to polymer matrix material (page 21 and pages 17-18). According to the rejection, "the antibodies are covalently attached to a polymer, wherein the polymer is in excess and would

result in at least 25 fold greater apparent weight as compared to the apparent size of the antibody fragment."

The rejection is respectfully traversed.

As cited before, the conjugates of the present invention are defined as heterogeneous molecules formed by antibody fragment(s) and nonproteinaceous polymer molecule(s), wherein the heterogeneous molecule is water soluble and free of any structured aggregate. In the context of the "conjugate" definition, "structured aggregate" is defined as () any aggregate of molecules in aqueous solution that assumes a spheroid or shell-shaped structure or (2) any aggregate of molecules in solid or insolubilized form that does not release the heterogeneous molecule into solution upon contact with aqueous phase. These definitions exclude antibody-conjugates chromatography beads, like those disclosed by Wicheck et al., from the scope of the present invention. Accordingly, claims 1-7 are not anticipated by the cited reference.

(2) Claims 1, 13, 18-22, and 28-31 were rejected under 35 U.S.C. § 102(e) as "being anticipated by Faanes et al. (U.S. Patent 5,695,760, filed 4/24/95). According to the rejection Faanes teaches "an antibody covalently conjugated to no more than one PEG40 kD molecule (see column 12, lines 62-63, column 22, lines 56-58, Table 1) wherein the apparent size of the conjugate is at least 500 kD (see column 19, lines 37-41) and the conjugate comprises a carrier that is sterile (see column 19, line 54 and column 20, line 20).

For a prior art to be applicable, its disclosure must be enabling for the subject matter for which it is used. The Faanes patent teaches the use of antibody PEGylation in order to reduce the immunogenicity of the PEG-derivatized antibody in an animal. Faanes et al. only exemplifies the PEGylation of full-length anti-ICAM antibody with 5 kD PEG (which is referred to as "preferred" throughout the disclosure). Faanes et al. describes the species particularly referred to in the Office Action only as part of an extremely broad genus.

In *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), the CCPA was faced with the issue of whether the subject of a claim (a species of an organic compound) was described by a relatively large genus inclusive of the species and by other species. The court held that the reference did not satisfy the written description requirement of 35 U.S.C. § 112. As the court explained:

> It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no hope in finding a trail . . . to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none.

Id. et 994-95, 154 USPQ at 122.

The court later stated:

> Working backward from a knowledge of chlorpropamide, that is, by hindsight, it is all very clear what route one would travel through the forest of the specification to arrive at it. But looking at the problem, as we must, from the standpoint of one with no foreknowledge of the specific compound, it is our considered opinion that the board was correct in saying:
>
> No having been specifically named or mentioned in any manner, one is left to selection from the broad disclosure, with no guidance indicating or directing that this particular selection should be made rather than any of the many others which could also be made.

Id. at 995, 154 USPQ at 123.

Just as in *Ruschig*, the Examiner has picked various "unmarked" statements from the disclosure of Faanes et al., using the disclosure of the present application as a guide post. Without this impermissible hindsight approach, based upon a fair reading of the entire Faanes disclosure, one would have had no reason to pick the particular disclosure cited by the Examiner in making the present rejection. Accordingly, applicants believe that the present rejection is legally improper, and should be withdrawn.

Claim Rejections - 35 U.S.C. § 103

(1) Claims 1-13, 15-16, 18-24, and 28-34 were rejected as "unpatentable" over Faanes et al. (U.S. Patent No. 5,695,760. According to the rejection, based on the disclosure of Faanes et al., which is analyzed on page 12 of the Office Action, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a conjugate consisting of PEG molecules attached to the antibody at various amount with various molecules weight PEG molecules.

The claims pending in this application are unified by the requirement that the apparent molecular weight of the claimed conjugates is at least about 500 kD. The claimed invention is

based on the inventors' discovery that a Fab' or $F(ab')_2$ conjugated to polyethylene glycol (PEG) molecules of 20 kD, 3 kD, or 40 kD exhibit greatly increased serum half-lives/reduced serum clearance rates compared to the unconjugated antibody fragments. The Fab'-PEG(40 kD) conjugate exhibited pharmacokinetics similar to full-length IgG. The serum clearance rate of the Fab'-PEG(40 kD) conjugate was 180-fold lower than the serum clearance rate of underivatized Fab'. The specification defines apparent size as the "molecular weight" of the conjugate as determined by gel exclusion chromatography against globular protein molecular weight standards. By this method, the apparent size of a Fab' is about 50 kD, and the apparent sizes of the Fab'-PEG(20kD) and Fab'-PEG(40kD) conjugates are about 540 kD and 1,800 kD, respectively. The claims pending in this application are crafted to cover such high "molecular weight" conjugates, which have unexpectedly superior clearance properties when compared to antibody fragments or conjugates that have lower apparent molecule weight. This is an invention that is nowhere taught or suggestion in Faanes et al.

As noted earlier, Faanes et al. prepare their conjugates to reduce the immunogenicity of antibodies in animals. Faanes only exemplifies the PEGylation of full-length anti-ICAM antibody using a 5 kD PEG molecule. Out of the 17 exemplified conjugates, only 3 did exhibit reduced immunoactivation in immunized animals as compared to underivatized parental antibody. Faanes did not characterize any structural features shared by the 3 successful conjugates. In the absence of such characterization, a skilled practitioner would not be able to reasonably predict success for any conjugates, and certainly not for conjugates using any size of PEG other than the 5 kD PEG that was successfully used in 3 out of 17 attempts. Indeed, the 5 kD PEG molecule is referred to as "preferred" throughout the Faanes disclosure, therefore, if anything, the use of this low molecular weight PEG species is taught by Faanes et al., at least for the purpose underlying their invention. Accordingly, contrary to the Examiner's position, Faanes et al. do not provide any motivation for a person skilled in the art to prepare conjugates with an apparent molecular weight of at least about 500 kD, as required by the claims pending in the present application. Nor would a person skilled in the art have a reasonable expectation of success to use such conjugates for the purpose disclosed in the present application based on the Faanes disclosure alone, without the benefit of the disclosure of the present application. As noted before, Faanes's objective by preparing their antibody conjugates is entirely different from the objective of the present inventors, and the results disclosed in Faanes et al. are inconsistent,

with a rather low success rate. In view of this, and in view Faanes's disclosure of the 5 kD PEG molecule as being preferred, a person skilled in the art would not have had any motivation to make the high molecular weight conjugates of the present invention, or any reasonable expectation of successfully using them, without undue experimentation.

In view of the foregoing arguments, the Examiner is respectfully requested to withdraw the present rejection.

(2) Claims 1-13, 15-25, and 28-34 were rejected under 35 U.S.C. § 103(a) as "unpatentable" over Faanes et al. and further in view of Zapata et al. (FASEB J. 9:A1476, 1995). Faanes et al. was cited as in the previous rejection. Zapata et al. was relied on for its teaching of the covalent attachment of MePEG to an antibody fragment of Fab' or $F(ab')_2$ through the single free thiol in the hinge region. According to the rejection, "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an antigen binding fragment with PEG attached in the hinge region as taught by Zapata et al. and producing a conjugate with the claimed characteristics as taught by Faanes et al."

Applicants have discussed the deficiencies of the disclosure of Faanes et al. in response to the previous rejection. Zapata et al. do not make up for these deficiencies. The Zapata et al. abstract teaches that an anti-CD18 Fab' derivatized with a single 5 kD or 10 kD PEG (through maleimide coupling to the free thiol in the hinge region of the Fab') yielded conjugates with 3-fold and 6-fold lower serum clearance rates, respectively , as compared to underivatized Fab'. Zapata et al. do not describe the use of large PEGs for construction of conjugates that would satisfy the size limitation of the claims pending in the present application. Although Zapata et al. suggest that some increase in serum half-life may be obtained by derivatizing Fab's with PEG molecules larger than 10 kD in size (the largest tested by the authors), the 6-fold decrease in serum clearance rate reported by Zapata et al. for the 10 kD PEGylated Fab' would not lead the practitioner to predict a 180-fold decrease in serum clearance rate by the Fab'-PEG(40 kD) conjugate of the present invention. Accordingly, the invention claimed in the present application results in substantially improved results over the cited combination of Faanes et al. and Zapata et al., and is, therefore, unobvious.

(3) Claims 1 and 33-34 were rejected under 35 U.S.C. § 103(a) as "unpatentable" over Faanes et al. and further in view of Harlow et al. Faanes et al. was cited as before. Harlow et al. for cited for its disclosure of radiolabeling antibodies.

Harlow et al. does not make up for the deficiencies of Faanes et al., since it has no disclosure, suggestion or hint for making and using high molecular weight conjugates, as disclosed and claimed in the present application. Accordingly, the cited combination provides no proper legal basis for the rejection of claim 1. Since claims 33-34 share the size limitation set forth in claim 1, they are not rendered obvious by the cited combination of Faanes et al. an Harlow for the same reasons. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

(4) Claims 1, 26 and 27 were rejected under 35 U.S.C. 103(a) as "unpatentable" over Faanes et al. "as applied to claim 1 above" and further in view of Doerschuk et al. (WO 95/23865). Doerschuk was cited for its teaching of an anti-IL-8 monoclonal antibody that binds human IL-8. According the rejection, "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a conjugate consisting of one or more antibody fragments covalently attached to one or more non-proteinaceous polymer molecules wherein the conjugate has an apparent size of at least about 500 kD taught by Faanes et al. with an antibody directed to human IL-8 as taught by Doerschuk et al."

As discussed above, Faanes et al. does not have an enabling disclosure for conjugates having an apparent size of at least about 500 kD. Since Doerschuk et al. has no teaching that would make up for this deficiency, the cited combination does not make obvious the rejected claims, and the withdrawal of the present rejection would be in order.

Applicants believe that all claims pending in this application are in prima facie condition of allowance, and an early action to that effect is respectfully solicited. Should the Examiner contemplate the maintenance of any of the current rejections, or intend to raise further issues, he is respectfully invited to contact the undersigned attorney at the telephone number shown below, so that a telephone or personal interview can be arranged.

Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: September 28, 2001

By: _____

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Version with markings to show changes made

In the Specification:

On page 1, the first sentence immediately following the title has been deleted, and replaced with the following new sentence:

-- This is a 35 U.S.C. §371 application of International Application No. PCT/US98/03337 filed February 20, 1998, now inactive, which claims priority under 35 U.S.C. §§120 and 365 to non-provisional application U.S. Serial No. 08/804,444 filed on February 21, 1997, now granted a U.S. Patent No. 6,117,980, and to its continuation-in-part application U.S. Serial No. 09/012,116 filed on January 22, 1998, now abandoned, of which the present application is a continuation.--

The paragraph starting at page 131, line 5 has been cancelled, and replaced with the following new paragraph:

-- The following biological materials have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, USA (ATCC): --

In the Claims:

Claim 14 has been amended as follows:

14. (Amended) The conjugate of claim 12, wherein the antibody fragment comprises a heavy chain and a light chain [derived from] corresponding to a portion of a parental antibody, wherein in the portion of the parental antibody the heavy and light chains are covalently linked by a disulfide bond between a cysteine residue in the light chain and a cysteine residue in the heavy chain, wherein in the antibody fragment the cysteine residue in the light or heavy chain is substituted with another amino acid and the cysteine residue in the opposite chain is covalently linked to a nonproteinaceous polymer molecule.